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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/671,089	09/27/2000	Daniel J. O'Mahony	E1067/20018	6019

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Marilou E. Watson
Synnestvedt & Lechner LLP
2600 ARAMARK Tower
1101 Market Street
Philadelphia, PA 19107-2950

EXAMINER

SNEDDEN, SHERIDAN

ART UNIT	PAPER NUMBER
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1653

DATE MAILED: 03/25/2003

14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/671,089	O'MAHONY ET AL.
	Examiner Sheridan K Sneden	Art Unit 1653

— The MAILING DATE of this communication appears on the cover sheet with the correspondence address —
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on _____.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-11 is/are pending in the application.
 - 4a) Of the above claim(s) 7-11 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1-6 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.
- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
 - a) The translation of the foreign language provisional application has been received.
- 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____.
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)
3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>9</u> .	6) <input type="checkbox"/> Other: _____

DETAILED ACTION

1. Applicant's election of invention I, claims 1-6 is acknowledged. Election was made with traverse in Paper No. 11. Claims 1-6 are under examination.

Applicant argues that an explanation was not provided as to burden of search to examine all the claims on the application. Applicant argues that it would not be a serious burden for the Examiner to search and examine the application in its entirety.

The above arguments are non-persuasive as the inventions are distinct for the reasons given in Paper No. 8 and the search required for Invention I is not required for Invention II-IV and the search required for SEQ ID NO: 2 is not required for SEQ ID NO: 3-24, restriction for examination purposes as indicated is proper.

2. The response submitted by Applicant in Paper No. 11 failed to elected a single peptide as required in Paper No: 8, mailed 9/30/2002. The elected invention I is directed to patentably distinct and/or independent peptides disclosed as SEQ ID NO: 2-24. Absent factual statement/evidence to the contrary, each different peptide sequence is considered distinct and/or independent, one from the other on the basis of physical, chemical and biological properties and function(s). Thus, when any one of the inventions I through IV is elected under 35 USC 121, an additional election under 35 USC 121 is also required as to the elected peptide (by SEQ ID NO). This selection of the peptide (and/or the polynucleotides encoding the peptide) by SEQ ID NO is not a species election.

3. During a telephone conversation with Marilou Watson on March 11, 2003 a provisional election was made with traverse to prosecute the invention of Group 1, claims 1-6, directed to a

peptide composition in as so far the invention relates to the peptide of SEQ ID NO: 2.

Affirmation of this election must be made by applicant in replying to this Office action.

Upon further consideration, SEQ ID NOs: 3 and 14-22 are rejoined to the present invention. Claims 7-11 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

4. Claims 1-6 and SEQ ID NOs: 2, 3 and 14-22 are under consideration.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for peptides of SEQ ID NO: 2, 3, and 14-22, does not reasonably provide enablement for all derivatives, fragments, analogs, motifs or peptidomimetic thereof. The specification does not give any guidance as to the full range of possible molecules which would possess the ability to enhance the membrane translocating characteristics of complexed agents.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a

disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

Each factor is addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

- 1) the nature of the invention;

In the instant case, applicants are claiming a peptides of SEQ ID NO: 2, 3, and 14-22 that posses the activity of enhancing the membrane translocation characteristics of particles or agents that are fused or complexed with the above peptides.

- 2) the breadth of the claims;

As recited, the claims are directed to all derivatives, fragments, motifs, analogs and mimetics of the above sequences that may be fused to all active agents and particles for the purpose of facilitating the membrane translocation of the agents or particles.

- 3) the amount of direction or guidance presented;

- 4) the presence or absence of working examples;

The instant specification teaches the sequences of SEQ ID NO: 2, 3, and 14-22 as possessing the desired properties and provides examples as such. The specification fails to define a motif or the minimal sequence or amino acids required that allows the peptides to function as membrane translocating sequences. For example, a fragment of SEQ ID NO: 2, as recited in claim 1, could consist of the dipeptide AA. It is unlikely that the fragment AA would possess membrane translocation properties.

- 5) the predictability or unpredictability of the art;

- 6) the state of the prior art;

Lin *et al.* teach the peptide of the like sequences, such as AAVLLPVLLAAP, as membrane translocating sequences. Ryser *et al.* teach the use of poly-Lysine, such as KK or KKK, and other cationic polymers that may be complexed with active proteins to facilitate membrane translocation. However, the prior fails to define a motif or the minimal sequence or amino

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acids, other than that described above, required that allows the peptides to function as membrane translocating sequences.

7) the quantity of experimentation necessary;

The courts have interpreted undue experimentation as requiring “ingenuity beyond that to be expected of one of ordinary skill in the art” (*Fields v. Conover*, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (*In re Colianni*, 195 USPQ 150 (CCPA 1977)). Additionally, the courts have determined that “... where a statement is, on its face, contrary to generally accepted scientific principles”, a rejection for failure to teach how to make and/or use is proper (*In re Marzocchi*, 169 USPQ 367 (CCPA 1971)). As such, given the guidance of the specification and the predictability of the art, the experimentation necessary to identify and qualify all fragments, motifs, derivatives and analogs of the above sequences possessing the ability to facilitate the translocation of fused agents is undue.

8) the relative skill of those skilled in the art;

In view of the discussion of each of the preceding seven factors the level of skill in this art is high and is at least that of a PhD or a person with several years of experience in the art. As the cited art would point to, even with a level of skill in the art that is high, predictability of the results is not invariable.

In consideration of each of factors 1 – 8, it is apparent that there is undue experimentation because of variability in prediction of outcome that is not addressed by the present application disclosure, examples, teaching, and guidance presented. Absent factual data to the contrary, the amount and level of experimentation needed is undue.

6. Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is also referred to the Guidelines on Written Description published at FR 66(4) 1099-1111 (January 5, 2001) (also available at www.uspto.gov).

Claims 1-6 are directed to a peptidomimetics of SEQ ID NO: 2. The specification discloses the protein of SEQ ID NOs: 2, 3 and 14-22, and general methods regarding how to

prepare the peptide. The specification does not provide all peptiomimetics of SEQ ID NOs: 2, 3 and 14-22, or guidance regarding how to obtain specific peptiomimetics that retain the function of the proteins defined as SEQ ID NOs: 2, 3 and 14-22.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the ‘written description’ inquiry, *whatever is now claimed.*” (See page 1117.) The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.” (See *Vas-Cath* at page 1116).

With the exception of SEQ ID NOs: 2, 3 and 14-22, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated proteins comprising the amino acid sequence set forth in SEQ ID NOs: 2, 3 and 14-22, but not the full breadth of the claim, meets the written description provision

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of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "substantially" in claims 1 and 2 is a relative term which renders the claim indefinite. The term "substanstialy" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claims 1-6 are rejected under 35 U.S.C. 102(e) as being anticipated by Lin *et al.* (US Patent 6,248,558). Lin *et al.* teach the peptide of the sequence AAVLLPVLLAAP which is identical to SEQ ID NO: 14 and comprises the sequences of SEQ ID NO: 15, 17-22. Lin *et al.* describes the above peptides as membrane-translocating peptide sequences (MTS). Lin *et al.* teaches that these peptides can be used to genetically engineer proteins with cell membrane permeability useful in therapy, such as cancer (see abstract). Lin *et al.* specifically teaches the peptide complexed to a molecular label and active protein (see claims 27-32). Additionally, as the peptide of maintains the biological function of the peptides set forth as SEQ ID NOs: 2, 3 and 14-22, the above protein is a peptidomimetic of the peptides of SEQ ID NOs: 2, 3 and 14-22. Thus, the reference anticipates the claimed invention.

10. Claims 1-6 are rejected under 35 U.S.C. 102(e) as being anticipated by Ryser *et al.* (US Patent 4,847,240). Ryser *et al.* teach the use of poly-Lysine, such as KK or KKK, and other cationic polymers that may be complexed with active proteins to facilitate their cellular transport or uptake into the cell. The poly-Lysine taught by Ryser *et al.* would fit the definition of a fragment or derivative of the peptides of the instant invention (see SEQ ID NO: 2 or 3, for example). Thus, the reference anticipates the claimed invention.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin *et al.* (US Patent 6,248,558) in view of Ryser *et al.* (US Patent 4,847,240).

Lin *et al.* teach the peptide of the sequence AAVLLPVLLAAP which is identical to SEQ ID NO: 14 and comprises the sequences of SEQ ID NO: 15, 17-22. Lin *et al.* describes the above peptides as membrane-translocating peptide sequences (MTS). Lin *et al.* teaches that these peptides can be used to genetically engineer proteins with cell membrane permeability useful in therapy, such as cancer (see abstract). Lin *et al.* specifically teaches the peptide complexed to a molecular label and active protein (see claims 27-32).

Ryser *et al.* teach the use of poly-Lysine, or KKK, and other cationic polymers that may be complexed with active proteins to facilitate their cellular transport or uptake into the cell.

Taken together, the above references teach a peptide of KKAAVLLPVLLAAP (SEQ ID NO: 2) or KKAAVLLPVLLAAP (SEQ ID NO: 3). It would have been obvious to the person of ordinary skill in the art at the time the invention was made to add a poly-Lysine polymer to the peptide of AAVLLPVLLAAP in order to make a peptide with membrane translocating properties, as both the AAVLLPVLLAAP peptide and poly-Lysine polymers are known to enhance the cell membrane permeability of proteins fused the above groups.

The rejections under 35 USC 103 above are consistent with case law. Applicants are referred to *In re Kerkoven* (205 USPQ 1069) in which it was shown to be *prima facia* obvious to combine two compositions, each of which is taught by the prior art to be used for that very same purpose. *Ex Parte Quadranti* (25 USPQ2d 1071) also sets forth this precedent, in that the use of materials in combination, each of which is known to function for the intended purpose, is

generally held to be *prima facia* obvious. *Ex parte Kucera* (165 USPQ 332) clearly states that synergism has no magical status in rendering otherwise obvious subject matter patentable. Therefore, then, barring unexpected results, one would reasonably expect enhanced, additive, or synergistic activity to be observed by combining the compositions or materials. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan K Snedden whose telephone number is (703) 305-4843. The examiner can normally be reached on Monday - Friday, 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone number for regular communications to the organization where this application or proceeding is assigned is (703) 746-3975.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

SKS
March 24, 2003

SKS

Karen Cochrane Carlson P.D.
KAREN COCHRANE CARLSON, PH.D.
PRIMARY EXAMINER